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One-year severity of depressive symptoms: Results from the NESDA study

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ABSTRACT

The aim of this study was to simultaneously examine a wide range of risk factors and clinical characteristics in their predictive value for the 1-year severity of depressive symptoms. Data from 789 participants in the Netherlands Study of Depression and Anxiety (NESDA), a large psychiatric cohort study, with a major depressive disorder (MDD) at baseline were used. Depression severity at 1-year follow-up was studied using linear and multinomial logistic regression models. Results of the analyses showed that high neuroticism, no partner and older age were found predictive of a poorer outcome independent of baseline clinical characteristics. Further, comorbid anxiety disorder, first episode, having a moderate subtype (vs. melancholic), and higher baseline depression severity predicted poorer outcome. To conclude, both risk factors and clinical characteristics independently predicted 1-year severity of depressive symptoms. The findings indicate that the prediction of prognosis and identification of persons at risk of a poor outcome should not only be based on clinical characteristics, but on risk factors as well.

1. Introduction

Whereas in the literature several etiologic and developmental models for major depressive disorder (MDD) have been proposed (Teasdale, 1988; Kendler et al., 2000, 2006; Beck, 2008; Sjoholm et al., 2009), the literature on prognostic models for MDD is relatively scarce. It has been proposed that etiologic factors that increase the risk of developing depression, like high neuroticism, may also play a role in the prognosis of the disorder, for instance, in the cognitive vulnerability theory and in the differential activation hypothesis (Teasdale, 1988). Several studies indeed found that neuroticism determined an unfavorable course (Enns and Cox, 1997; Spijker et al., 2001; Mulder, 2002; Rhebergen et al., 2008). Risk factors other than personality have also been associated with depression outcome. For instance, childhood trauma and recent stressful life events have been associated with a more chronic depression trajectory (Kessler, 1997; Wiersma et al., 2009). Other factors such as a family history of MDD or absence of a partner have been found to predict poorer course, although not consistently (Keller et al., 1984; Bagby et al., 2002; Trivedi et al., 2006; Husain et al., 2009). Further, the presence of comorbid somatic diseases has been associated with less favorable depression outcomes (Bagby et al., 2002; Esposito and Goodnick, 2003; Spijker et al., 2004; Trivedi et al., 2006), while factors like gender, age, race and socio-economic status have been inconsistently associated with depression course (Keller et al., 1984; Simpson et al., 1997; Spijker et al., 2001; Bagby et al., 2002; Esposito and Goodnick, 2003; Hollon et al., 2006; Trivedi et al., 2006; Kaptein et al., 2007).

Although these risk factors have thus been shown to possibly affect the course of depression, no previous study of persons with a current depression has thoroughly examined whether risk factors are important course predictors independent of psychiatric indicators at baseline, or whether their predictive value is completely explained by differences in baseline clinical characteristics. By studying risk factors and clinical characteristics simultaneously, better knowledge will be obtained about the unique contribution of various risk and clinical indicators to the course and prognosis of depression. This information may aid clinicians in more efficient identification of those at high risk of a poor course, can be helpful in choosing the best suited treatment strategy, and makes that patients could be provided with better information about their prognosis.

The aim of the present study in a large cohort of 789 adults with MDD was to simultaneously examine a wide range of risk factors as well as clinical characteristics in their predictive value for the one-year severity of depressive symptoms. We expected that effects of risk factors would largely be mediated by clinical characteristics.

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2. Methods

2.1. Study sample

Data were derived from the Netherlands Study of Depression and Anxiety (NESDA), a prospective, longitudinal cohort study ($N=2981$) aimed at examining the long-term course of depressive and anxiety disorders. The cohort consists of persons with current or remitted depressive and/or anxiety disorders (6-month current, $n=1701$; remitted $n=628$) and healthy controls ($n=652$). Participants, aged 18–65 years, were recruited from the community ($n=564$, 19%), primary care ($n=1610$, 54%) and specialized mental health care ($n=807$, 27%). In primary care, all persons consulting their GP in the last 4 months irrespective of reason for consultation were screened for the presence of depression and anxiety symptoms (Kessler-10 with additional questions regarding symptoms of anxiety), and when having a positive score, invited for a diagnostic interview, after which persons with a confirmed diagnosis were invited to participate. In specialized mental health care settings, all newly enrolled patients were invited to participate in the NESDA. All participants recruited from the community ($n=564$) previously participated in longitudinal studies (NEMESIS (Bijl et al., 1998) ARIADNE (Landman-Peeters et al., 2005; Penninx et al., 2008)). Exclusion criteria used in the NESDA were (1) a primary clinical diagnosis of a psychiatric disorder not under study in the NESDA and that would be expected to affect course trajectory: psychotic disorder, obsessive compulsive disorder, bipolar disorder, or severe addiction disorder, and (2) not being fluent in Dutch. More details about the design and recruitment of the NESDA study are reported elsewhere (Penninx et al., 2008). Approval of the study protocol was granted by the Ethical Review Board of the VU University Medical Center and all participants gave written informed consent. The baseline assessment included a 4-hour interview in which information on a wide range of domains was collected, like psychopathology, demographic characteristics, physical and psychosocial functioning and further included a medical assessment, computer tasks and two self-administered questionnaires. At 1-year follow up, participants filled out a self-administered questionnaire to determine the course of anxiety and depressive symptoms.

For the present study, all persons with a current (1 month recency) DSM-IV major depressive disorder (MDD) ($n=802$) at baseline were selected. The presence of MDD was assessed using the Composite International Diagnostic Interview (CIDI), WHO version 2.1 (World Health Organization, 1997). The CIDI is a reliable and valid instrument to assess DSM-IV depressive diagnoses(Wittchen, 1994), and was assessed by specially trained research staff. Of the selected sample ($n=802$), 13 persons (1.6%) had missing data on the depressive symptom assessment both at baseline and at 1-year follow-up and were subsequently excluded for the present analyses. Of the remaining respondents ($n=789$), 194 (25%) did not provide data for the dependent variable, the Inventory of Depressive Symptomatology (IDS), at the 1-year follow-up. Those with missing data were younger (39.3 vs. 42.6 yrs, $p=0.001$), less educated (10.4 vs. 11.6 yrs, $p<0.001$), more often of non-North-European descent (12.1% vs. 5.6%, $p=0.002$) and had lower rates of recurrent depression (44.7% vs. 52.9%, $p<0.05$) than those who had no missing data. No differences between groups were found for any of the other indicators of MDD (e.g. subtype of MDD, baseline IDS score, duration of symptoms, age at onset), or for age, gender and other demographics. Because case deletion may introduce bias, it is preferable to maintain information from persons with missing data by using techniques that impute data for missingness based on all available data and account for missing-data uncertainty (Schafer and Olsen, 1998; Sinharay et al., 2001). Therefore, the sample which we report on in the present study consists of the 789 persons with MDD at baseline.

2.2. Severity of depressive symptoms

The Inventory of Depressive Symptomatology self-report version (Rush et al., 1996) was used to assess symptom severity at baseline and at 1-year follow-up. The questionnaire consists of 28 items on depressive symptoms rated on a 4-point scale. The summed score ranges from 0 to 84, with higher scores indicating a higher depression severity. The validity and reliability of the IDS have been shown to be satisfactory (Rush et al., 1996). Mean number of days between the two assessments was 394 days (S.D. 73).

Along with the IDS score at 1-year follow-up, a second outcome measure was constructed, representing extreme groups that are of specific interest from a clinical point of view, namely remitters and persons with severe symptom severity after 1 year. In this categorical variable, one category consisted of persons with an IDS score<14 at 1-year follow-up, representing a group of remitted persons (Rush et al., 2003). A second category consisted of persons who had an IDS score>38 at follow-up, representing a group with severe symptoms and thus poor outcome (Rush et al., 2003). The third category comprised all persons scoring mild to moderate depressive symptoms at follow-up, which served as the reference group.

2.3. Determinants of depressive symptoms at 1-year follow-up

2.3.1. Risk factors

Family history was assessed using the Family Informant Schedule and Criteria (Mannuzza et al., 1985). Respondents were asked whether family members ever had a depression, and those reporting first-degree family members (parents or siblings) with depression were considered to have a positive family history. Childhood trauma was defined using the structured inventory from the NEMESIS study that constructs an index (range 0–4) incorporating the occurrence and frequency of four types of abuse before age 16 (emotional neglect, psychological abuse, physical abuse and sexual abuse) (Wiersma et al., 2009). A count of negative life events in the past year was constructed based on a list of 12 negative life events (Brugha et al., 1985). Neuroticism was assessed using the NEO-Five-Factor Inventory (Costa and McCrae, 1995). Further, during the interview, respondents were asked about the presence of 21 somatic chronic diseases. A count of these diseases was made, representing the somatic health status of respondents. Years of education, partner status (yes/no), gender, age and ethnic background (North-European descent – yes/no) were assessed in the baseline interview.

2.3.2. Baseline clinical characteristics

Duration of depressive symptoms at baseline (or chronicity) was assessed by the life chart interview which used a calendar method to determine life events during the past 4 years to refresh memory, and then presence of depressive symptoms during the past 4 to 5 years was assessed (Lyketsos et al., 1994). From this information, the cumulative number of months with depressive symptoms was calculated and transformed into a percentage of time with depressive symptoms in the prior 4 years before baseline. Information on age at onset of first full syndrome as determined with the CIDI interview (<21 yrs vs. ≥21 yrs) and single versus recurrent episodes (more than 1 episode during lifetime) was derived from the CIDI. Subtype of MDD was based on a classification of depressive subtypes derived from a latent class analysis (LCA) among NESDA respondents (Lamers et al., 2010). In this LCA study, we identified three different symptom profiles that were labeled as a melancholic severe subtype, an atypical severe subtype, and a moderate severe subtype, based on symptom probabilities. Comorbid anxiety disorders were defined by the CIDI as presence of DSM-IV classified panic disorder, agoraphobia, social phobia or generalized anxiety disorder in the past month. Also the past month presence of a DSM-IV diagnosis of alcohol dependence was derived from the CIDI. Finally, current severity of depressive symptoms was assessed at baseline with the IDS (Rush et al., 1996; Trivedi et al., 2004).

2.4. Statistical analyses

All analyses were performed using SPSS, version 17, and for all analyses two-tailed tests were used with $\alpha=0.05$. To evaluate the associations of variables with depressive symptoms, linear regressions were performed with 1-year IDS as the dependent variable and baseline IDS score as the covariate. First a model with risk factors was run to evaluate the predicting value on 1-year depressive symptoms irrespective of clinical characteristics. Likewise, a second model only included clinical characteristics. Finally, risk factors and clinical characteristics that had a $p<0.10$ in previous models were joined in a third model to evaluate the independent prognostic effect of these variables on the change in depressive symptoms. We used the cut-off of $p<0.10$ to minimize the chance of missing any relevant variables in multivariable analyses. Multicollinearity of variables in the models was checked by evaluating the VIFs, and no multicollinearity problems were found. A similar stepwise approach was used in the multinomial logistic regression models, with the categorized depression status at 1 year as outcome.

Because missing data result in loss of power and often introduce bias because of selective response, multiple imputation (MI) was performed. Multiple imputation is a technique in which for each missing value a set of $m>1$ plausible values are drawn from their predictive distribution (Rubin, 1987; Schafer and Olsen, 1998). Because it can account for the uncertainty of missing values, multiple imputation is considered to be a better alternative than other imputation methods (Sinharay et al., 2001). With the SPSS multiple imputation option, 10 imputed data sets were generated, using the fully conditional specification (FCS) method. Generally, 3 to 10 imputations are considered to obtain good results, and will suffice even with 40–50% missing information (Rubin, 1987; Sinharay et al., 2001). Results from the analyses of the 10 separate datasets were pooled, correcting the standard errors of the regression coefficients for within-imputation variability and between-imputation variability (Rubin, 1987). The use of imputation techniques for missing data in longitudinal cohort studies is desirable but not yet a standard procedure in psychiatric research, although more and more studies use MI in their analyses (Brotman et al., 2007; Carney et al., 2008; Brent et al., 2009). We therefore checked the consistency of results in conservative analyses in which we only used data from persons with completed 1-year IDS scores.

3. Results

Table 1 shows the baseline characteristics of the sample ($n=789$). Sixty-six percent of the sample were women and the mean age was 41.8 years (S.D. 12.0). The mean baseline IDS score was 36.0 (S.D. 11.2), whereas at 1-year follow-up the mean IDS score was 26.6 (S.D. 13.0). Of the initial sample, 18% had remitted (IDS<14), 19% was severely depressed (IDS>38), and the majority (63%) had mild to moderate symptoms at 1-year follow-up (Table 1).

Analyses of the predictive value of risk factors on 1-year severity of depressive symptoms, controlled for baseline severity, revealed that childhood trauma, higher neuroticism, not having a partner and older age were significantly associated with a higher IDS score, representing higher depression severity at 1-year follow-up (Table 2, model 1). Of the clinical characteristics, longer duration at baseline and comorbid anxiety disorders were significantly associated with a higher IDS score

Table 1
Baseline characteristics of study sample ($N = 789$).

Risk factors		
Family history depression (%)		79.2
Childhood trauma, mean (S.D.)		2.3 (2.4)
Number of negative life events in past year, median (IQR)		0 (1)
Neuroticism, mean (S.D.)		43.2 (6.5)
Number of chronic diseases, median (IQR)		0 (1)
Education (yrs), mean (S.D.)		11.3 (3.2)
Having no partner (%)		36.9
Female gender(%)		66.2
Age, mean (S.D.)		41.8 (12.0)
North European ancestry (%)		92.8
Baseline clinical characteristics		
Duration at baseline(percentage of 4 yrs), median (IQR)		33.9 (45.1)
Late onset (≥21yr) (%)		61.6
Recurrent MDD (%)		50.8
Depressive subtype (%)	Melancholic	48.5
	Atypical	26.1
	Moderate	25.4
Comorbid alcohol dependence (1 mo) (%)		6.0
Comorbid anxiety disorders (1 mo) (%)		62.7
Clinical setting (%)	Community	7.0
	Primary care	37.8
	Specialized mental health	55.3
TCA use (%)		3.7
SSRI use (%)		30.2
Other antidepressant use (%)		10.7
Psychotherapy (%)		47.1
Depressive symptoms measures		
Baseline IDS score, mean (S.D.)		36.0 (11.2)
1-yr FU IDS score, mean (S.D.)		26.6 (13.0)
1-yr FU status (%):	Remitted	18.3
	Mild-moderate symptoms	62.5
	Severe symptoms	19.2

Table 2
Pooled regression coefficients for IDS at 1-year follow-up ($n = 789$).

		Model 1		Model 2		Model 3	
		β (se)	P	β (se)	P	β (se)	P
Risk factors							
Family history depression		−0.836 (1.006)	0.41				
Childhood trauma		0.395 (0.179)	0.03			0.321 (0.174)	0.07
Number of life events (past yr)		−0.128 (0.374)	0.73				
Neuroticism		0.279 (0.082)	<0.001			0.231 (0.085)	<0.01
Number of chronic diseases		0.718 (0.428)	0.094			0.707 (0.422)	0.09
Education (yrs)		−0.256 (0.152)	0.096			−0.184 (0.151)	0.23
Not having a partner		2.396 (1.004)	0.02			2.095 (1.015)	0.04
Female gender		−0.285 (0.978)	0.77				
Age		0.107 (0.037)	<0.01			0.106 (0.037)	<0.01
North European ancestry		−1.771 (2.082)	0.40				
Baseline clinical characteristics							
Duration at baseline (per% increase)				0.038 (0.016)	0.02	0.026 (0.016)	0.11
Late onset (>21 yr)				0.552 (0.958)	0.57		
Recurrent MDD				−1.820 (0.878)	0.04	−2.095 (0.867)	0.02
Depressive subtype	Melancholic			Ref			
	Atypical			−0.762 (1.000)	0.45		
	Moderate			−0.653 (1.269)	0.61		
Clinical setting	Primary care			Ref			
	Specialized mental health			−0.698 (1.000)	0.49		
	Community			−0.559 (1.699)	0.74		
Comorbid alcohol dependence				3.084 (1.869)	0.10		
Comorbid anxiety disorders				2.538 (0.973)	0.01	1.937 (1.018)	0.06
TCA use				−1.466 (2.298)	0.52		
SSRI use				−0.003 (1.052)	0.99		
Other antidepressant use				1.879 (1.443)	0.19		
Psychotherapy				0.301 (0.876)	0.73		
Baseline severity							
IDS score (per point increase)		0.523 (0.045)	<0.001	0.576 (0.046)	<0.001	0.491 (0.044)	<0.001

while recurrent MDD was associated with a lower IDS score (model 2). Notably, setting and treatment variables were not associated with IDS score at 1-year follow-up. In the third model, including all variables with a p-value<0.10 in previous models, most variables remained significant predictors of a higher depression severity, with the exception of childhood trauma, duration of depression at baseline and comorbid anxiety, although comorbid anxiety was marginally associated with a higher IDS score in this model. The estimate of childhood trauma decreased with 18%, indicating mediation by clinical characteristics. Baseline depressive symptom severity was a strong predictor of one-year depressive severity in all models. The explained variance (R square) of the models in the 10 imputed datasets ranged from 0.34 to 0.38 for model 1 and 2, and from 0.37 to 0.40 for model 3.

Along with the continuous outcome measure, we evaluated a categorical variable in which we compared a group of persons with mild-moderate depression after 1 year with those who had remitted (IDS<14) and those who had severe depression (IDS>38). Of the risk factors, only younger age was significantly associated with remission and this association was marginally significant ($p = 0.09$) in the full model (model 3, Table 3). Of the clinical characteristics the absence of comorbid anxiety disorder, moderate subtype of depression (compared to the melancholic subtype) and a lower baseline severity were associated with a higher relative risk of remission. Higher neuroticism and higher baseline severity were significantly associated with a higher relative risk of being severely depressed at 1-year. The explained variance (Nagelkerke) of the models in the 10 imputed datasets ranged from 0.33 to 0.37 for model 1, 0.35 to 0.37 for model 2 and 0.35 to 0.38 for model 3.

Multiple imputation was performed because approximately 25% of the sample had missing IDS data at 1-year follow-up due to non-response. Applying the step-wise analytical approach in the original, non-imputed dataset led to the inclusion of recurrent depression to the logistic regression model. Also, in the original data, number of chronic diseases was not included in model 3 of the logistic regression, but otherwise all other outcomes were highly comparable (data not shown).

4. Discussion

This study evaluated the associations of both risk factors and clinical characteristics on the severity of depressive symptoms at 1-year follow-up in a cohort of patients with MDD. Our study showed that several risk factors were predictive of a poorer outcome after 1 year, independent of baseline clinical characteristics. High neuroticism was a predictor of

Table 3
Pooled relative risks (95% confidence intervals) for remission after 1 year, and for presence of severe symptoms after 1 year (reference group are those with mild-moderate symptoms after 1 year) ($n=789$).

		Remitted after 1 year (IDS<14)			Severe symptoms after 1 year (IDS>38)		
		Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Risk factors							
Family history depression		0.96 (0.54–1.71)			0.76 (0.44–1.32)		
Childhood trauma		0.96 (0.87–1.06)			1.05 (0.95–1.15)		
Number of life events (past yr)		0.96 (0.78–1.18)			1.00 (0.79–1.27)		
Neuroticism		0.98 (0.96–1.02)		0.98 (0.94–1.03)	1.07 (1.02–1.12)‡		1.06 (1.01–1.12)†
Number of chronic diseases		0.77 (0.57–1.04)*		0.79 (0.58–1.08)	1.11 (0.89–1.38)		1.15 (0.93–1.43)
Education (yrs)		1.08 (0.99–1.17)*		1.07 (0.99–1.17)	1.00 (0.93–1.08)		1.00 (0.93–1.08)
Not having a partner		0.63 (0.38–1.07)*		0.63 (0.37–1.07)*	1.36 (0.86–2.14)		1.41 (0.89–2.21)
Female gender		0.85 (0.51–1.44)			0.88 (0.54–1.44)		
Age		0.98 (0.96–0.99)†		0.98 (0.96–1.00)*	1.01 (0.99–1.03)		1.01 (0.99–1.04)
North European ancestry		1.44 (0.45–4.62)			0.74 (0.31–1.79)		
Baseline clinical characteristics							
Duration at baseline (per% increase)			0.99 (0.98–1.01)			1.01 (0.99–1.01)	
Late onset (>21 yr)			0.91 (0.56–1.47)			1.27 (0.78–2.07)	
Recurrent MDD			1.34 (0.81–2.24)			0.68 (0.42–1.12)	
Depressive subtype	Melancholic		Ref	Ref		Ref	Ref
	Atypical		1.38 (0.74–2.59)	1.23 (0.65–2.34)		1.14 (0.68–1.89)	1.12 (0.67–1.89)
	Moderate		1.82 (0.99–3.33)*	1.94 (1.06–3.57)†		1.61 (0.63–4.13)	1.56 (0.61–4.00)
Setting	Primary care		ref	ref		ref	ref
	Specialized mental health		2.09 (1.19–3.64)†	1.69 (0.97–2.93)*		1.33 (0.79–2.24)	1.44 (0.86–2.41)
	Community		1.43 (0.60–3.44)	1.41 (0.61–3.26)		0.81 (0.26–2.49)	0.75 (0.24–2.37)
Comorbid alcohol dependence			0.84 (0.30–2.38)			1.74 (0.69–4.42)	
Comorbid anxiety disorder			0.55 (0.35–0.89)†	0.57 (0.35–0.95)†		1.31 (0.73–2.33)	1.32 (0.73–2.38)
TCA			0.92 (0.22–3.84)			0.79 (0.26–2.45)	
SSRI			0.67 (0.37–1.19)			0.95 (0.55–1.63)	
Other Antidepressants			0.62 (0.24–1.56)			1.48 (0.69–3.20)	
Psychotherapy			0.98 (0.60–1.60)			0.95 (0.59–1.55)	
Baseline severity							
IDS score (per point increase)		0.93 (0.90–0.96)‡	0.94 (0.91–0.97)‡	0.94 (0.91–0.97)‡	1.10 (1.07–1.13)‡	1.12 (1.09–1.15)‡	1.10 (1.07–1.14)‡

‡ $p<0.01$.
† $p<0.05$.
* $p<0.10$.

poorer outcome in both analyses, while older age and lack of a partner were predictors of poorer outcome in linear regression analyses, and were marginally associated with remission in the logistic regression. Of the clinical characteristics, higher baseline severity predicted poorer outcome. Having a first episode (versus a recurrent episode) was also associated with poorer outcome, but only in linear regression analyses. Comorbid anxiety lowered the chance of remission, while having a moderate subtype (compared to the melancholic subtype) increased the chance of remission.

One of the reasons for performing these analyses is that, although risk factors have often been found to predict course of MDD, these were often not studied in concert with other predictors of course like clinical characteristics, leaving question marks about which risk factors are associated with course independent of clinical characteristics. The NESDA study – with its extensive data collection – allowed for the evaluation of a large set of risk factors and clinical characteristics within a large sample of persons with MDD. We found that the effects of not having a partner, older age and higher neuroticism were independent of clinical characteristics. Our study showed that high neuroticism was associated with poorer outcome at 1-year follow-up even when clinical characteristics were taken into account, implying that neuroticism has a unique influence on outcome of MDD. Most other studies found similar findings, but rarely included potential predictive clinical characteristics in their models (Mulder, 2002). Several studies have shown that not having a partner predicted poor outcome in univariable but not in multivariable analyses (O'Leary et al., 2000; Trivedi et al., 2006). We found that not having a partner was an independent determinant for more depressive symptomatology after 1 year, and was marginally associated with a lower chance of remission. With respect to age, previous studies found mixed results. In contrast to findings of Spijker and colleagues who found younger age to be associated with poor outcome after 1 year (Spijker et al., 2001), we found younger age to be marginally associated with remission and older age to be associated with higher levels of depressive symptoms after 1 year. We further observed that the effect of childhood trauma on depression severity weakened and was no longer significant when analyzed simultaneously with clinical characteristics. As previous research showed that childhood trauma is associated with a longer duration of MDD(Wiersma et al., 2009), which itself was a significant predictor of poorer outcome, the weakened effect of childhood trauma is not surprising. Also, the effect of the number of chronic diseases on the relative risk of having severe symptoms was no longer significant when clinical characteristics were taken into account. However, this is in contrast with findings from other studies showing that having more physical diseases was associated with poorer course in multivariable analyses including depression severity (Spijker et al., 2004; Trivedi et al., 2006).

Of the clinical characteristics, comorbid anxiety disorder is a well-known determinant of unfavorable course of MDD (Bagby et al., 2002; Kaptein et al., 2007). In the current study we found that for persons with comorbid anxiety disorder the chance of remission was 43% lower than in persons without comorbid anxiety. In contrast with previous studies (Klein et al., 2006; Rhebergen et al., 2008), we found that longer duration of MDD at baseline did not predict higher IDS scores at follow-up after inclusion of risk factors to the model. The finding that a higher depression severity at baseline was associated with a higher relative risk on poor course and a lower relative risk on remission is also in accordance with previous studies (Keller et al., 1992; Melartin et al., 2004; Iacoviello et al., 2006; Trivedi et al., 2006; Blom et al., 2007; Iacoviello et al., 2007; Conradi et al., 2008). While studies have reported that recurrent episodes are generally more

severe and indicative of a worse longitudinal course (Bagby et al., 2002; Hollon et al., 2006; Roca et al., 2011), in the NESDA, however, having a first episode predicted a worse course, although only in linear regression analysis. This finding may be partially explained by the fact that symptom severity – which is increasing with number of episodes (Roca et al., 2011), and a predictor of poor outcome – was also included in the model. Further, in the NESDA a relatively large number of persons had a first episode with a long duration, and in fact the percentage of time with depressive symptoms in the 4 years prior to baseline was significantly higher in persons with a first episode compared to persons with recurrent episodes. Persons with a first episode may thus be just as affected as persons with recurrent episodes, and this may explain our finding that persons with a first episode had a poorer outcome. Surprisingly, none of the treatment variables (tricyclic antidepressants, selective serotonin reuptake inhibitors, other antidepressants or psychotherapy) was associated with outcome, nor was recruitment setting in the final models. An additional analysis with a combined variable for any type of treatment (yes/no) also showed no association with symptoms after 1 year.

Several limitations of this study need to be noted. We studied relatively short-term outcome of severity (1-year follow-up), meaning that the identified predictors are not per se also predictors of long-term severity of depressive symptoms. The assessment of severity of depression at 1-year follow-up does not further inform us about the fluctuations of severity during the year, that are likely to have occurred (Judd, 1997). Thus, we do not know for how long the MDD in the remitted group had been absent, leaving unclear how many of these persons were indeed in remission according to the frequently used definition of no significant signs or symptoms for at least 2–4 consecutive weeks (Keller, 2003; Rush et al., 2006). Likewise, we cannot distinguish between those who were chronically depressed versus those who had been in remission during some time of the follow-up and subsequently developed relapse or recurrence prior to the assessment at 1-year follow-up. Finally, because 25% of the sample had missing data, and non-responders tended to be younger, less educated, less often of North-European descent and less often had recurrent depression, analyzing only persons with complete follow-up data would lead to biased outcomes. Multiple imputation (MI) was therefore performed to impute missing data in an effort to overcome such bias. Generally, within MI, 3 to 10 imputations are considered to obtain good results, even with 40–50% missing information (Rubin, 1987; Sinharay et al., 2001). As mentioned in the results, analyses of persons with complete data showed highly comparable results.

This study showed that only a limited number of risk factors and clinical characteristics were predictive of 1-year severity of depressive symptoms in persons with MDD. Along with those with more severe MDD, comorbid anxiety first episode or moderate subtype, persons who are older, persons without a partner, and persons with high neuroticism may experience more severe depressive symptoms and may require closer monitoring in daily practice. Assessment of these risk factors in patients with MDD may aid clinicians in predicting a patient's prognosis and may aid decisions on the intensity and duration of treatment. The risk factor childhood trauma on the other hand appeared to be largely mediated through more unfavorable clinical characteristics at baseline.

To conclude, within a large cohort of MDD patients both risk factors and clinical characteristics independently predicted 1-year severity of depressive symptoms. This implies that the prediction of prognosis and the identification of persons at risk of a poor outcome should not only be based on clinical characteristics, but on risk factors as well.

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